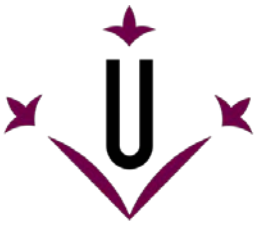

Basal cell carcinoma of the vulva: immunohistochemical analysis of four cases report.

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common tumour in Caucasians and is usually localized in sun-exposed body areas as face or trunk. The localization of BCC in genitalia is atypical, but we have to consider this diagnosis when we find a lesion in vulva. The most common vulvar malignancy is squamous cell carcinoma (SCC) that can develop from vulvar intraepithelial neoplasia (VIN) or de novo. (Chokoeva AA. Vulvar cancer: a review for dermatologists). Vulvar BCCs are not related to human papillomavirus (HPV) infection as other tumours located in this area as SCC or VIN. In fact, the detection of HPV could be used to distinguish BCC from basaloid SCC. (Elwood H et al. Basal cell carcinomas of the vulva: high risk human papillomavirus DNA detection, p 16 and BerEP4 expression. Am J Surg Pathol.). Women over 60 years are the main affected, chronic vulvar irritation could be a risk factor. (Kara M et al. Vulvar basal cell carcinoma. Indian J Pathol Microbiol.).

Patients usually consult because they present itch or bleed in the vulva and in the moment of the examination we find a tumour as the cause of their symptoms. The clinical image and prognosis of vulvar BCC are quite different from others BCC such as those in face or trunk. Gynaecologists are very often the first specialist in visiting these patients with an ulcerative plaque in vulva that require confirmation about the type of tumour. It is important to note that BCC in vulvar semimucosa can get confused with other neoplasms (malignans and benigns).

In this work, we describe four vulvar BCCs from three patients. Three of these cases are located on the inner aspect of the labia majora, a hairless skin area. In these cases, we have also described the expression pattern of different

markers by immunohistochemistry. Based on our data, we discuss about the characteristics of these infrequent BCCs.

CASE REPORTS

In Dermatology Department we have found four cases of genital BCC throughout a year. The first case was a 62 years old woman, who consulted for a lesion located in the vulva, in the third posterior of the labia majora, near the fourchette, that had appeared one year ago. It was an indurated, smooth, ulcerated, shiny plaque, that measured 13x9 mm. Histological examination showed a superficial BCC. The second case was a woman 66 years old with a vulvar lesion that had bled several times for the last two months. It consisted of an indurated and eroded plaque of 1.5 cm, located in the inner aspect of the labia majora, containing pigmented areas on the periphery (Figure 1a). Once removed, the biopsy showed that it was a superficial BCC (Figure 1b). After 3 years we review the scar of the previous genital BCC we appreciated a little ulcerative plaque next to the previous BCC scar. We took a biopsy of the lesion and the result was a superficial BCC. The third case was an 86 years old woman, having a medical history of several facial BCC. She checked for two vulvar papulonodules on each sides of the vulva that she had for three months. The lesions settled also in the vulvar semimucosa, in the hairless area, and measured 0.5 and 0.7 cm in diameter (Figure1c, and not shown). The biopsy showed that they were nodular BBC (Figure 1d, and not shown).

We studied by immunohistochemistry the four vulvar. The antibodies (DAKO, Glostrup, Denmark) used were against: CK5/6 (clone D5/16 B4) which is expressed in the basal keratinocytes of stratified epithelia; CK7 (clone OV-TL 12/30) and CK19 (clone RCK108) both present in the simple epithelium with

glandular differentiation such as eccrine and apocrine glands; β-catenin (clone β-Catenin-1) as BCC marker; and p63 (DAK-p63) as a stem cell marker. Slides were counterstained with hematoxylin. Microscopic analysis was performed by two independent observers (M.R.G and F.V.). The degree of expression was graded as follows: -, negative; +, weakly positive; ++, strongly positive; +++, very strongly positive. The results are shown in Table 1. The four vulvar BCC were positive for CK5/6, β-catenin and p63 that are expressed in the majority of BCC, but also genital BCC express CK 7 and CK19.

DISCUSSION

The location of a BCC in the vulvar region is very rare. Until now 300 cases have only been described. They represent the 0.01-1.75% of BCC and 2-7% of vulvar carcinomas (1) and show a more aggressive behaviour given thatrecurrences and metastasis are more frequently develop Currently, nine metastatic cases (approximatively, 3,0%) have been published from genital BCC (Perrone T, 1987; Hoffman MS, 1988; Winkelmann SE, 1990; Gleeson NC, 1994; Mizushima J, 1995; Benedet JL, 1997; Feakins RM, 1997; Mulayim N, 2002; Blok JL, 2012), but considering all the BCC the prevalence of any metastatic site is only 0.0028 to 0.55%. This data supports the relevance in the study of vulvar BCC.

In vulvar area we can find other malignancies as Paget's disease. Paget´s disease is an uncommon intraepidermal carcinoma where Paget cells are found in the histological analysis. Old patients are the mainly affect. Normally the first symptom is icth as sometimes happens in vulvar BCC and in the physical examination we can find scaly plaques. The origin of Paget´s disease could be primary, that means a cutaneous origin. But Paget´s disease also can be

secondary, with a origin in a visceral malignancy as in anorectum or colon when Paget´s disease appears in anogenital area. Cytokeratin profile could be useful to distinguish primary Paget´s disease from the secondary type. Primary Paget´s disease usually express CK7 and GCDFP 15 whereas secondary Paget´s disease also express CK7, but also CK20. CK 20 is not expressed in primary Paget´s disease. Another immunohistochemical differency is in GCDFP 15 that is positive in the primary type and negative en the secondary type (Suthiwartnarueput W. Primary perianal Paget´s disease… J Med Assoc Thai.).

Trichoblastoma is a benign tumour, normally appears in neck or in head, but a vulvar trichoblastoma has been described in vulvar area recently. The histological analysis is very similar with basal cell carcinoma, so the immunohistochemical study can be useful in some cases. Differential diagnosis from basal cell carcinoma can be difficult but is facilitated using immunohistochemistry. (Pina A et al. Vulvar trichoblastoma. J Low Genit Tract Dis). Trichoblastoma normally express CK5/6, CK14, CK17, CK19. The expression of CK7, CK8, CK13, CK18, CK20, alpha-smooth-muscle actin is normally negative. Basal cell carcinoma could present in some cases the same profile, so (Schirren CG et al. Trichoblastoma and BCC… Am J Dermatopathol.) the he treatment of trichoblastoma is the excision with negative margins.

The four vulvar BCCs expressed CK5/6, p63 and β-catenin. The expression of p63 and β-catenin is found in many tumours not only skin. However all the vulvar BCCs showed expression of CK7 and CK19. Even the most accepted theory that explain the origen of BCC located the original cell in hair follicle. At the same case that vulvar BCC, the expression of CK7 and CK19

has been observed in different carcinomas derived from the glandular epithelium as sebaceous carcinoma, or apocrine glands as extra-mammary Paget's disease and multiple adnexal tumours of vulvar location.

The most accepted theory about its origin is that BCC results from mutations induced by ultraviolet radiation on stem cells from hair follicle and mechanosensory niches (3). It is important to note that three of the vulvar BCCs studied in this work were located in non-hairy area (inner aspect of labia majora). Then, the epithelium of apocrine or sebaceous glands that are abundantly represented in vulvar skin and in hairless semimucosa of labia majora may participate on the origin of vulvar BCC. In agreement with this hypothesis we have observed high expression of CK7 in the four vulvar BCCs. Alessi et al, 2010 described that in nodular BCC the expression of CK7 was not frequent but 15 out 17 of BCC with glandular differentiation were CK7 positive. These authors propose that BCCs can also be originated in stem cells of apocrine units.

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Table 1. Immunohistochemical Pattern.[a]

Case	CK5/6	CK7	CK19	β-Catenin	p63
Case 1	++	+++	+	++	++
Case 2	+++	+++	++	++	+++
Case 3a	++	++	++	++	+++
Case 3b	++	++	++	++	+++

[a]Intensity levels: –, negative; +, mild; ++, moderate; +++, high.

Figure legends

Figure 1.

Clinical features from vulvar BCC above and its histological appearence immediately below.

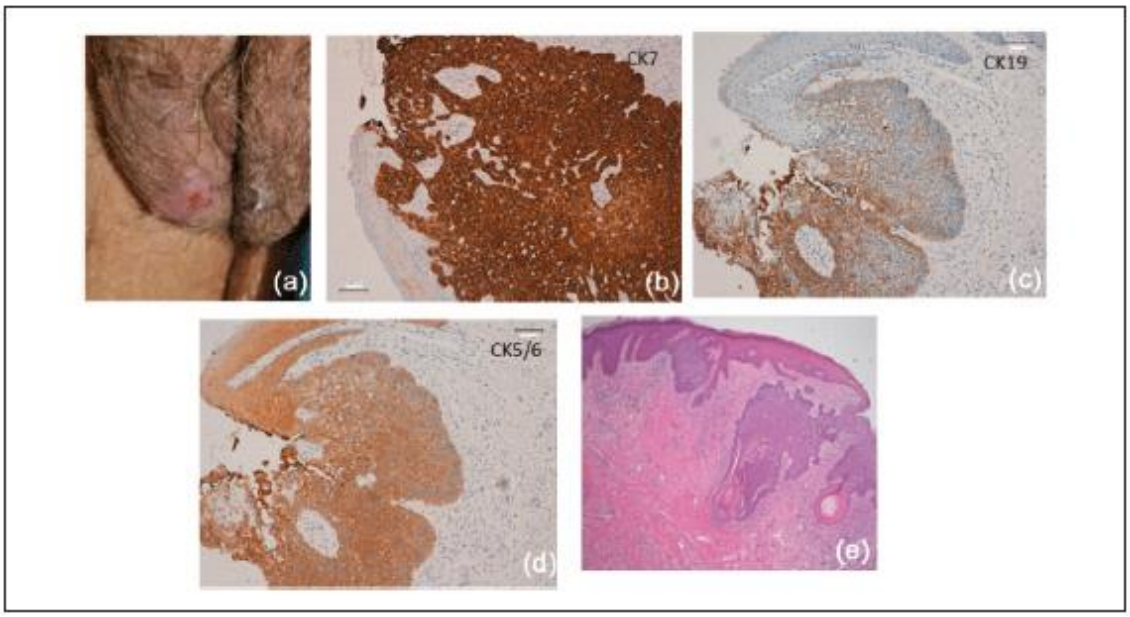
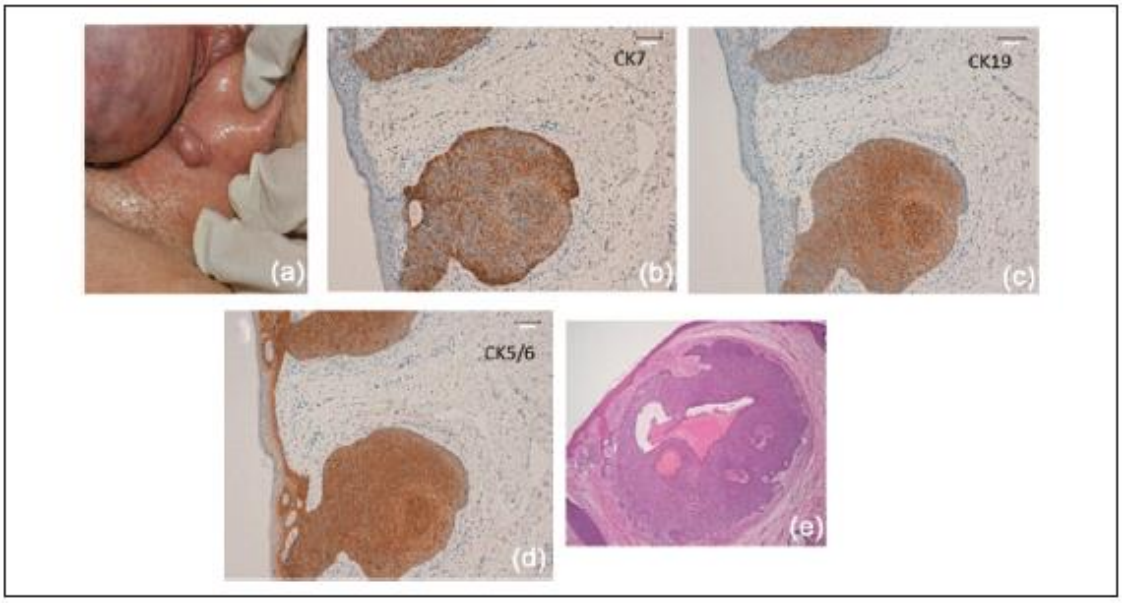


Figure 2.

Case-control comparison: Vulvar BCC on the left, with positivity for CK7 and CK19 on the immunohistochemical study; facial BCC on the right, with negativity for CK7 and CK19 on the immunohistochemical study. Both BCC correspond at the same patient, who has a large history of BCC.


(a)
CK7
(b)
CK19
(c)
CK5/6
(d)
(e)